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REVIEW ARTICLE

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Neoplastic fever: a neglected paraneoplastic syndrome

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Abstract Neoplastic fever, a paraneoplastic syndrome caused by cancer itself, represents a diagnostic challenge for the clinician and is an important issue in supportive oncology. Timely recognition of this febrile condition by differentiating it from other cancer-associated fevers, such as infection and drug reaction, is essential for effective patient management. Although the pathophysiology of neoplastic fever is not well understood, it is suspected to be cytokine mediated. In clinical practice, when a patient with cancer presents with unexplained fever, extensive diagnostic studies are needed to differentiate neoplastic fever from nonneoplastic fever. Only after excluding identifiable etiologies of fever can the diagnosis of neoplastic fever be suspected. According to our experience, the naproxen test is a safe and useful test in differentiating neoplastic fever from infectious fever in patients with cancer. In addition, naproxen and other nonsteroidal anti-inflammatory drugs have been effective in the management of neoplastic fever and offer a significant palliative benefit for the patient.

Keywords Neoplastic fever · Fever palliation · Fever of unknown origin · Naproxen test · Analgesics · Antipyretics

Introduction

Although long overdue, the importance of supportive care has finally gained the attention of cancer care workers. Good supportive care is an integral part of cancer treatment and undoubtedly contributes to an improved quality of life for the patient. Considerable strides have been made in the management of cancer over the past two decades with earlier diagnosis, a better understanding of tumor biology, and advances in antineoplastic treatments, including chemotherapy, radiation therapy, biological agents, and recently introduced targeted therapies. However, these treatment modalities have their limitations in improving patient quality of life and survival in certain patients, and their associated side effects and expenses may outweigh their benefits. Accordingly, supportive care has emerged as an important issue in the overall management of cancer.

Managing cancer-related symptoms, including pain, fatigue, anorexia, weight loss, depression, and specific cancer-site-related symptoms, has gained importance in delivering high-quality cancer care. Neoplastic fever is another common cancer-related paraneoplastic syndrome, and it not only poses a diagnostic dilemma in patients with cancer, but it also causes significant morbidity [12, 15, 47]. Furthermore, the management of neoplastic fever has not been addressed sufficiently in the palliative care arena.

Fever in patients with cancer

Fever in patients with cancer is a serious concern and usually indicates the presence of an infection. Fever was commonly seen in patients with cancer in the era of less intensive antineoplastic therapy [12, 47], and now is much more common—especially with the advent of more aggressive chemotherapy. "Neutropenic fever" in the patient with neutropenia following intensive chemotherapy is a common occurrence in clinical practice. Even in the absence of infection, chemotherapy, or other cancer-related treatments, fever has been seen in patients with newly diagnosed cancer. Cancer was the cause of fever in approximately 20% of cases of fever of unknown origin (FUO) in an earlier report [33], and recent studies have shown that cancer was the cause of FUO in about 15% of cases [58].

Neoplastic fever, which is defined as fever caused by cancer itself, has been shown to be the most common cause of FUO in patients with cancer [15]. The febrile patient with cancer, particularly one who has received recent chemotherapy, presents the clinician with a challenging search for the cause of fever. Initial consideration must be directed at common conditions, e.g., infections, perhaps related to marrow suppression and immunocompromised state, and febrile drug reactions due to chemotherapeutic and non-chemotherapeutic agents. If all the potential causes of fever are excluded, the possibility of neoplastic fever should be considered. It is well known that Hodgkin's disease, non-Hodgkin's lymphomas, acute leukemias, and renal cell carcinomas frequently present with neoplastic fever, but it has been observed that almost any other cancer can cause neoplastic fever [8, 43]. Establishing the correct diagnosis of neoplastic fever allows for rational clinical intervention, the avoidance of unnecessary treatments and extensive diagnostic tests (thus saving medical care expenses), and provides palliation of fever-related morbidity. Early recognition of neoplastic fever is imperative, inasmuch as prolonged fever, with an uncertainty about its etiology, is stressful both psychologically and physically for the patient and family as well as the physician.

The differential diagnosis for fever in patients with cancer is broad, and the various causes of fever in patients with cancer are presented in Table 1. After fever due to infection, neoplastic fever represents the next most common etiology in chemotherapy-naive patients. Fever due to the administration of certain chemotherapeutic agents, such as bleomycin, daunorubicin, cisplatin, asparaginase, streptozocin, and interferons, the newer monoclonal antibodies including rituximab and alemtuzumab, and also growth factors such as sargramostim and filgrastim, is common [1, 2, 4, 11, 13, 32, 45, 49, 53, 54].

Defining neoplastic fever

No clinical features reliably differentiate neoplastic fever from fever due to infection, fever associated with autoimmune diseases, or fever due to other causes. Therefore, neoplastic fever is a diagnosis of exclusion, typically established after exhaustive evaluation and exclusion of other causes of fever in the patient with cancer. Clinical manifestations of neoplastic fever have been described. Typically, fever due to infection, particularly in the immunocompromised patient, presents with spiking temperatures and is associated with chills, warmth, and periodic sweating. Tachycardia, hypotension, and occasionally mental changes may be seen, particularly in gram-negative bacteremia. On the other hand, neoplastic fever is usually characterized by a sensation of warmth and sweating, but manifests with less chills than other types of fever. Tachycardia and mental changes are lacking or mild. In contrast to fever due to infection, neoplastic fever is less responsive to acetylsalicylic acid and acetaminophen, but exhibits a more dramatic response to nonsteroidal anti-inflammatory drugs [21]. Although these clinical findings are important in raising the clinical suspicion of the neoplastic origin of fever, they are not reliable enough to ascertain the diagnosis in clinical practice.

Objective methods, other than extensive studies to exclude infections and other causes of fever, have been introduced to help differentiate between fever due to infection and neoplastic fever. The nitroblue tetrazolium test was used to differentiate between fever due to bacterial infection and that due to nonbacterial infection [29, 46]. However, this test was subsequently determined to have

Table 1 Causes of fever in cancer patients

Causes	Examples
Infections	Bacterial, viral, fungal, and parasitic
Neoplastic origin	Renal carcinoma, acute leukemias, Hodgkin's lymphoma, and others
Chemotherapy-induced	Bleomycin, daunorubicin, cisplatin, asparaginase, and interferons
Blood transfusion reaction	
Drug reaction	Drug fever
Central nervous system metastasis	Hypothalamic involvement, meningeal leukemia, and meningeal carcinomatosis
Radiation-induced	Radiation pneumonitis and radiation pericarditis
Adrenal crisis	Steroid-induced adrenal insufficiency

little value [19]. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used nonspecific markers of inflammation, and, recently, these tests have been investigated as potential markers for differentiating fever due to an infection from neoplastic fever [37]. C-reactive protein and ESR levels on admission and follow-up CRP levels (done on hospital day 5) were compared in 66 hospitalized patients, 56 with fever due to infection and 10 with neoplastic fever [37]. These investigators found that CRP and ESR levels at admission were not clinically useful in differentiating neoplastic fever from fever due to infection [37]. However, follow-up CRP levels were significantly lower in patients with fever due to infection when compared with those with neoplastic fever [37].

The antipyretic activity of naproxen has been well documented as first described more than 25 years ago [14, 39]. The naproxen test was first described by Chang and Gross in 1984 as a reliable method in differentiating neoplastic fever from nonneoplastic fever in patients with cancer [20]. After an extensive hospital in-patient evaluation for prolonged unexplained fever (i.e., more than 7 days) in 20 patients with cancer and two with connective-tissue disease, these patients were treated orally with 250 mg naproxen twice daily. In the initial report, 14 of 15 patients with neoplastic fever had a complete, sustained lysis of fever while being treated with naproxen. None of five patients with fever due to infection had defervescence, and two patients with connective-tissue disease had partial lysis of fever [20]. In patients with neoplastic fever, the fever lysis was complete within 24 h, and the afebrile state was sustained as long as the patients were maintained on naproxen. Typically, defervescence was followed by profuse diaphoresis for a few hours, and then an obvious symptomatic improvement, which was apparent within 24 h. Side effects were minimal and generally limited to gastrointestinal discomfort. The naproxen test was useful, but it was recommended that a thorough clinical examination as well as the appropriate laboratory and imaging studies be performed, and an adequate empiric antibiotic treatment be given for at least 5 to 7 days before the consideration of using the naproxen test. Table 2 shows the proposed diagnostic criteria for neoplastic fever.

Indomethacin, ibuprofen, diclofenac, and other nonsteroidal anti-inflammatory drugs also have been shown to be useful in treating neoplastic fever [44, 56]. Reports from a small case series suggest that rofecoxib was useful for treating neoplastic fever in patients with cancer who had contraindications to naproxen [38]. In this study, all six patients with neoplastic fever achieved complete lysis of fever after treatment with rofecoxib [38]. The recent withdrawal of rofecoxib from the market by its manufacturer due to increased risks of cardiovascular events halted the clinical use of this medication [36]. This action placed the further use of rofecoxib in the diagnosis and treatment of neoplastic fever on hold.

Table 2 Diagnostic criteria for neoplastic fever

I. Temperature over 37.8°C at least once each day
II. Duration of fever over 2 weeks
III. Lack of evidence of infection on
A. Physical examination
B. Laboratory examinations, e.g., sputum smears or cultures, cultures of blood, urine, stool, bone marrow, spinal fluid, pleural fluid, and discharge from local lesions
C. Imaging studies, e.g., chest radiograph and computed tomographic scans of the head, abdomen, and pelvis
IV. Absence of allergic mechanisms, e.g., drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction
V. Lack of response of fever to an empiric, adequate antibiotic therapy for at least 7 days
VI. Prompt, complete lysis of fever by the naproxen test with sustained normal temperature while receiving naproxen

Corticosteroids have been shown to cause the suppression of fever caused by various etiologies, including allergic reactions, collagen vascular diseases, infections, and malignancy [10, 22, 25, 28, 40]. The antipyretic effect of corticosteroids on neoplastic fever was compared to that of naproxen [16]. In this retrospective study, naproxen treatment resulted in the complete lysis of neoplastic fever in 36 (90%) of 39 patients [16]. On the other hand, a separate treatment of 12 of these patients with corticosteroids resulted in lysis of fever in 6 patients (i.e. 50%) [16]. Although it is important to note that the sample size of this study was small and that it was not a controlled clinical trial, naproxen was shown to be more effective for neoplastic fever than corticosteroids.

Utility of the naproxen test

Follow-up data on the efficacy of the naproxen test included a total of 68 cancer patients with FUO [15]. Further statistical analysis of these data provides important insights into the value of the naproxen test. In the aforementioned report, 50 of 68 patients had neoplastic fever in the final analysis; thus, the prevalence of neoplastic fever in this series was 74% [15]. Further interpretation should then be considered in light of this high prevalence of neoplastic fever. The 18 other patients described included 13 with infectious fever, 4 with autoimmune-disease-related fever, and 1 with radiation-related fever [15]. Out of 50 patients with neoplastic fever, there were 46 complete responses (complete lysis of fever), 2 partial responses, and 2 patients with no response to naproxen (i.e., persistent fever) [15]. Among 13 patients with infectious fever, 1 partial response to naproxen was noted, and 12 patients had no response to naproxen [15]. Out of 4 patients with autoimmune-disease-related fever, 2 had partial responses and 2 had no response [15]. The 1 patient with radiation-related fever did not

respond to naproxen. Calculation of the sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals (CI) for the naproxen test on the aforementioned data is performed here, using widely available internet-based statistical calculators [60]. By comparing complete response vs no response/partial response in the aforementioned study, the following can be calculated for the characteristics of the naproxen test: sensitivity is 92% (95% CI, 80–97%), specificity is 100% (95% CI, 78–100%), the positive predictive value is 100% (95% CI, 90–100%), and the negative predictive value is 82% (95% CI, 59–94%). Thus, in this population of patients with cancer with a high clinical suspicion for neoplastic fever, the complete lysis of fever after the naproxen test is highly predictive of true neoplastic fever (i.e., the positive predictive value approaches 100%). It is critical to emphasize that the suspicion for neoplastic fever in cancer patients afflicted with fever must be high (i.e., high prevalence) for the naproxen test to have such high utility (i.e., high positive predictive value).

The usefulness of the naproxen test has been confirmed by others in patients with neoplastic fever associated with advanced gynecologic malignancies [27], and this test also has been recommended by several authors in the evaluation of patients with FUO [3, 24, 48]. One study has challenged the use of the naproxen test as a diagnostic method to establish neoplastic fever in patients presenting with prolonged fever [59]. This was a small retrospective analysis examining a cohort with a low prevalence of neoplastic fever (only 11 patients, or 14%, had neoplastic fever in the final analysis) [59]. The authors report no significant difference between a positive naproxen test in patients with neoplastic disorders compared to those with nonneoplastic disorders (55% vs 38%, p=0.5) [59]. However, it is important to note that this was a study of the naproxen test in cases of FUO, but not in cases of cancer patients with FUO. In addition, with such a small sample size, this study was not powered to detect a difference between these groups even if a difference existed. Despite these limitations, the study exemplifies the importance of having a high clinical suspicion for neoplastic fever based on careful clinical examination and laboratory investigation before subjecting patients to the naproxen test.

Pathophysiology of neoplastic fever

Although investigations have aimed at understanding mechanisms involved in neoplastic fever, the pathophysiology is still uncertain. Nonetheless, the mechanism for neoplastic fever seems to be distinct from the mechanism for fever due to infection. Earlier studies demonstrated the presence of pyrogens in the urine and tissues of cancer-associated febrile patients [50, 55]. Other studies showed that tumor cells from patients with neoplastic fever produced a pyrogen in vitro [8, 9]. Subsequent research suggested the potential involvement of various cytokines. The major pyrogenic cytokines released by cancer cells include interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and interferon [26, 42]. The same cytokines, however, can produce infectious fever or neoplastic fever in the patient with cancer [42]. These cytokines activate the anterior preoptic nuclei of the hypothalamus and raise the set point for body temperature through the induction of prostaglandin E2 [42]. In patients with renal cell carcinomas, increased serum IL-6 levels have been associated with an increased incidence of neoplastic fever and also with advanced stage, poor performance status, and decreased responsiveness to immunotherapy [6, 7]. In lymphomas, high levels of IL-6 and IL-10 have been observed, and the presence of B-symptoms correlates with serum levels of IL-6 [52]. Molecular investigations of cytokine deregulation have been conducted in acute lymphoblastic leukemia and juvenile chronic myelogenous leukemia cell lines [5]; however, no direct causal relation to neoplastic fever has been established at the molecular level.

Other mechanisms for neoplastic fever include tumor necrosis, which some investigators have attributed to the release of TNF and other pyrogens from dead tissue [35]. Bone marrow necrosis, for example, is due to malignancy in the majority (>90%) of cases, and fever has been documented in 68% of cases of bone marrow necrosis [34]. Bone marrow necrosis may cause the release of toxins and cytokines from damaged cells [34]. For example, elevated plasma levels of TNF were detected in two patients with metastatic tumor to the bone marrow and bone marrow necrosis [41]. Neoplastic fever in patients with brain metastases is suspected to be one example of neurogenic fever [35], which has been attributed to direct brain tissue damage and subsequent activation of phospholipase A2 [35, 61]. Despite all of the aforementioned associations, specific mechanisms for cytokine-mediated neoplastic fever induction have not been established. Thus, presently, the exact pathophysiology of neoplastic fever and its difference from other causes of fever remain uncertain.

Proposal for the diagnosis of neoplastic fever

Initial steps for establishing the diagnosis of neoplastic fever in patients with cancer include a careful clinical history and physical examination followed by appropriate laboratory studies (including serial blood cultures, also, cultures of sputum, stool, spinal fluid, local skin lesions/drainage, pleural or peritoneal fluid, urine, urinalysis, and complete blood count as indicated) and imaging studies (e.g., chest films, computed tomography scans, and magnetic resonance imaging scans). After these initial diagnostic steps, the following decision tree is recommended, which is illustrated in Fig. 1. While awaiting laboratory results, an empiric treatment with standard broad-spectrum antibiotic monotherapy (e.g., third- or fourth-generation

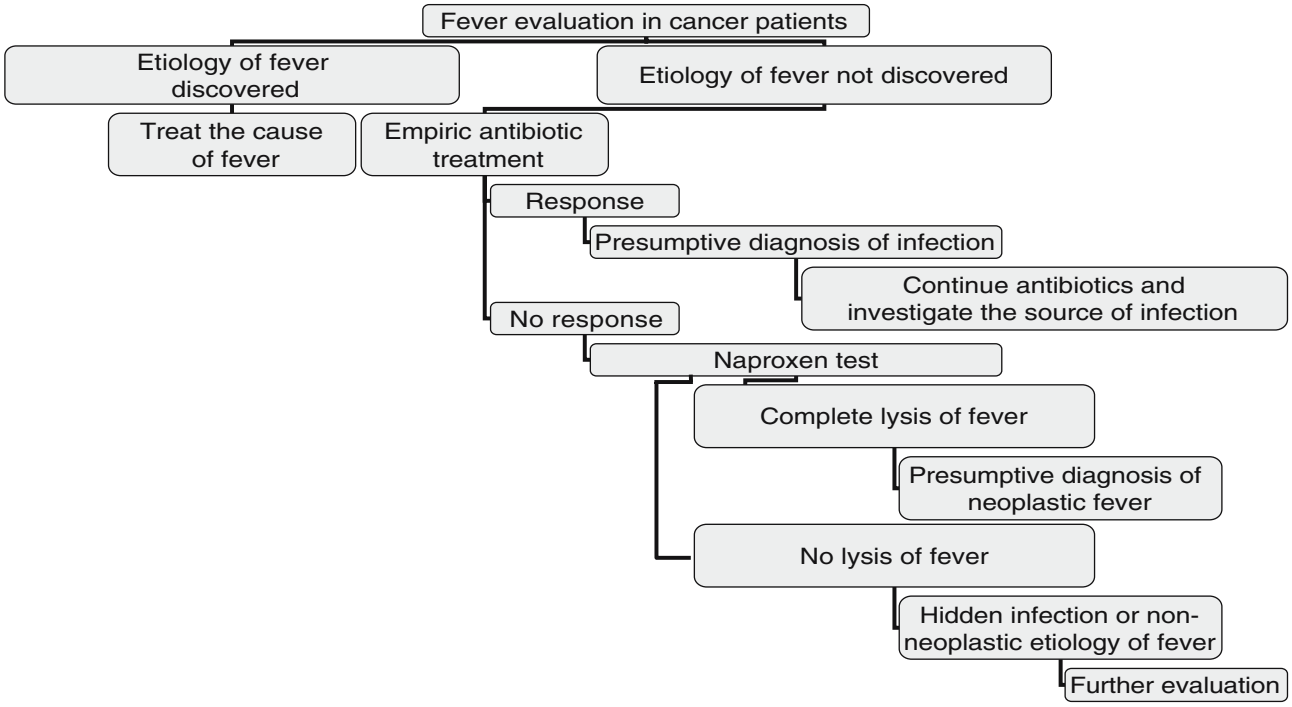

Fig. 1 Proposal for the diagnosis of neoplastic fever in cancer patients. (Adapted with permission from Chang 1989 [17])

cephalosporins, carbapenems, and piperacillin–tazobactam) or combined therapy (e.g., second-generation cephalosporins with aminoglycosides), with or without vancomycin in certain circumstances [31], is warranted for at least 7 days. During this time, the clinical response and febrile course should be monitored closely. If a definite clinical response is noted, although the source of infection is not identified, antibiotic(s) must be continued with a presumptive diagnosis of fever due to an infection, and further investigations in search of the source of infection should be continued. If no clinical response to antibiotics occurs and there are no contraindications (e.g., a platelet count less than 30,000/μL), the naproxen test can be initiated with 375 mg orally every 12 h, for at least a 36-h period [18].

Antibiotic treatments may be continued during the naproxen test and will not interfere with the results [18]. The complete lysis of fever indicates a positive response to the naproxen test, which should establish a presumptive diagnosis of neoplastic fever. However, although false positives are rare, the patient should be monitored closely during naproxen treatment to rule out fever due to an infection or other nonneoplastic etiology. Persistent fever after naproxen treatment strongly suggests fever due to an infection or other nonneoplastic etiology, and further evaluation must be continued. By following this decision tree for febrile patients with cancer, including the administration of the naproxen test, we were able to make the diagnosis of neoplastic fever with a high sensitivity and specificity.

Neutropenic fever

Neutropenic fever is a common complication of intensive chemotherapy regimens, and it also occurs in chemo-naive patients with bone marrow failure particularly in the setting of acute leukemias or metastatic tumors to the bone marrow. Currently, growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF) are used routinely to lessen the duration of neutropenic fever. In the initial US studies on the efficacy of filgrastim in a group of patients with small-cell lung cancer receiving chemotherapy, the use of filgrastim was shown to reduce the proportion of patients having at least one episode of febrile neutropenia and was also shown to reduce the duration of grade IV neutropenia [23]. Similarly, fewer episodes of febrile neutropenia and fewer delays in the treatment of patients with small-cell lung cancer treated with filgrastim were noted in the original European trials [57]. In addition, pegfilgrastim has been shown to reduce the incidence of febrile neutropenia and grade IV neutropenia in patients with breast cancer treated with chemotherapy in the first cycle and subsequent cycles to comparable levels achieved with filgrastim in a phase III study [30].

After chemotherapy, approximately 50% of cases of febrile neutropenia are due to occult or established infection, and about 20% of severely neutropenic patients (i.e., those with an absolute neutrophil count $<0.5\times10^9$ per

liter) with fever are bacteremic [51]. The remaining patients with persistent fever (with and without recovery from neutropenia) in the absence of an identifiable infection are a clinical dilemma. The usefulness of the naproxen test in patients with neutropenic fever of unknown origin (N-FUO) has been investigated [15, 18, 20, 21]. In these series of febrile patients with cancer, neoplastic fever was found to be the cause in most patients by the naproxen test. The naproxen test has been shown to be safe and effective in cases of N-FUO [15, 18, 20, 21]. However, severe thrombocytopenia due to chemotherapy-induced myelosuppression was a limiting factor for the use of naproxen in some patients.

Palliating neoplastic fever

Fever in cancer patients can be extremely distressful and is often associated with fatigue and confusion. In addition, fever of an unknown source demands intensive clinical examinations and diagnostic tests, which add more discomfort to already distressed patients. Disease-specific palliative chemotherapy may control neoplastic fever, with significant palliation of symptoms if the tumor is responsive to the treatment. The steroid component of a palliative chemotherapy regimen may be useful to palliate neoplastic fever by defervescence. However, our experiences indicate that nonsteroidal anti-inflammatory drugs seem to provide a safer and more effective palliation for distressful neoplastic fever. Naproxen, indomethacin, diclofenac, ibuprofen, and rofecoxib all have been used with varying but significant efficacy in the treatment of neoplastic fever [38, 56]. When naproxen was compared with indomethacin, ibuprofen, and diclofenac, it was noted that naproxen provided the most rapid response [56]. Additional benefits of naproxen treatment include a diagnostic differentiation between neoplastic and nonneoplastic fever and a durable response while the patient is taking the medicine. After complete lysis of fever, the naproxen dose may be decreased to the lowest possible dose for fever control and palliation if an extended treatment duration is desired. If naproxen is used, the potential benefit of symptomatic palliation should be weighed against possible side effects, such as gastritis and gastrointestinal bleeding, especially in the thrombocytopenic patient. Additional relative contraindications for naproxen use may include patients with significant cardiac, renal, and hepatic dysfunction. On occasion, subnormal temperatures have been observed in the first day of naproxen administration, especially in Hodgkin's disease and lymphomas, but in our experience these episodes were short-lived and have not resulted in any detrimental effect to the patient. Although the data are limited to one small case series, in cases of thrombocytopenia, rofecoxib provided a reasonable alternative for the palliation of neoplastic fever [38].

In some patients, neoplastic fever will recur if naproxen is discontinued after a short-term treatment. Such recurrent fever may lead to repeat diagnostic studies in some practices, resulting in an expensive and futile exercise. In a previous study of recurrent fever in patients with neoplastic fever, although naproxen induced sustained fever lysis in some patients, the fever returned to pretreatment levels in 7 of 10 patients after naproxen withdrawal [21]. This recurrence of fever typically occurred within 24 h after naproxen withdrawal [21]. In cases of recurrent fever shortly after successful treatment of neoplastic fever with naproxen, the subjective history may reveal that the patient is not compliant. Retreatment with naproxen typically results in complete and sustained fever lysis—obviating the need for expensive diagnostic evaluation. However, if the recurrent fever is not resolved with the reintroduction of naproxen, a reevaluation for infection and other causes is warranted.

Conclusions

In a febrile patient with cancer, establishing the correct diagnosis of neoplastic fever remains the cornerstone for effective management. To this aim, the naproxen test can be used to aid in the differentiation of neoplastic fever from nonneoplastic fever. Furthermore, once the diagnosis of neoplastic fever is established, naproxen and other anti-inflammatory agents can be an effective tool for symptom palliation. The safety and efficacy of the treatment are well established, and the side effects are not a significant issue. Depending on circumstances, naproxen may be used as a bridge to subsequent definitive cancer-targeted therapy, or it may be used in the supportive and palliative care setting for those patients who are not candidates for further chemotherapy.

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